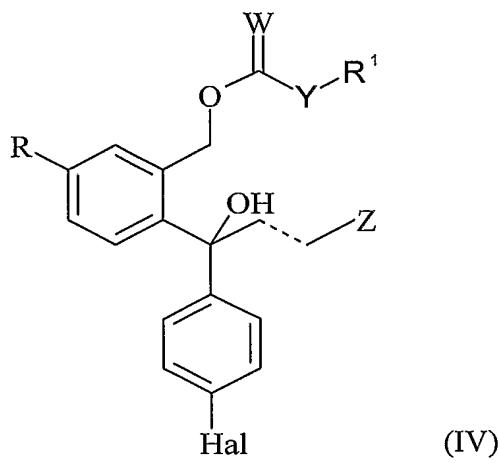


Claims:

1. A method for the isolation and purification of the compound having a formula



5

wherein R is cyano or a group which may be converted to a cyano group,

the dotted line represents a double or single bond,

Hal is halogen,

10 Z is a dimethylaminomethyl group or Z is a group which may be converted to a dimethylaminomethyl group,

W is O or S,

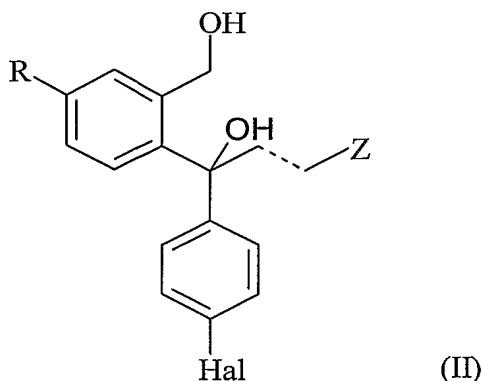
Y is a bond, O, S or NH,

and R¹ is C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl or C₂₋₁₀-alkynyl all of which may optionally be

15 substituted with one or more substituents selected from C₁₋₁₀-alkoxy, C₁₋₁₀-alkylthio, hydroxy, halogen, amino, nitro, cyano, C₁₋₁₀-alkylamino, di-(C₁₋₁₀-alkyl)amino, aryl, aryloxy, arylthio and heteroaryl, or R¹ is aryl, wherein any of the the aryl and heteroaryl groups may optionally be substituted one or more times with substituents selected from C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₁₋₁₀-alkoxy, C₁₋₁₀-alkylthio,

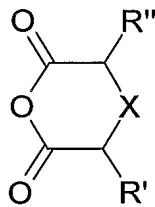
20 hydroxy, halogen, amino, nitro, cyano, C₁₋₁₀-alkylamino and di-(C₁₋₁₀-alkyl)amino, or a salt thereof,

and/or a diol of formula



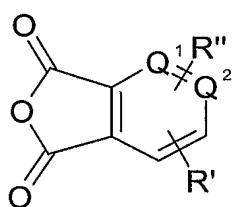
wherein R, Z, Hal and the dotted line are as defined above, or a salt thereof, from a mixture containing the compound of formula (IV) and the diol of formula (II), which
5 comprises:

a) reacting said mixture containing the compound of formula (IV) and the diol of formula (II) with a cyclic anhydride or imide of formula

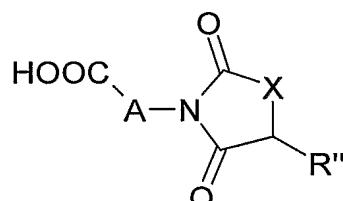


(Ia)

or



(Ib)



(Ic)

10

wherein X is $-(\text{CH}_2\text{CH}_2)_n-$, wherein n is 0-2;

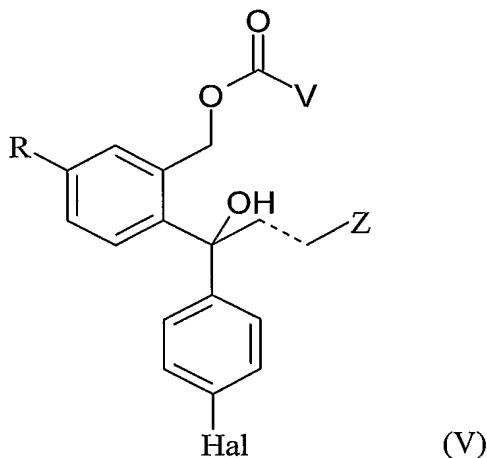
and R', R'' and R''' are independently selected from hydrogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, aryloxy, C₁₋₆-acyloxy, aryl-CO-O, wherein each aryl may be substituted with C₁₋₆-alkyl, or R' and R'' in an anhydride of formula (Ia) together are $-\text{O}-\text{CR}^4\text{R}^5-\text{O}-$, wherein R⁴ and R⁵ are independently hydrogen or C₁₋₆-alkyl, or R' and R'' in an anhydride of formula (Ib) are adjacent and together with the two carbon atoms to which they are attached form a benzene ring;

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one of Q¹ and Q² is nitrogen and the other carbon, or both are carbon;

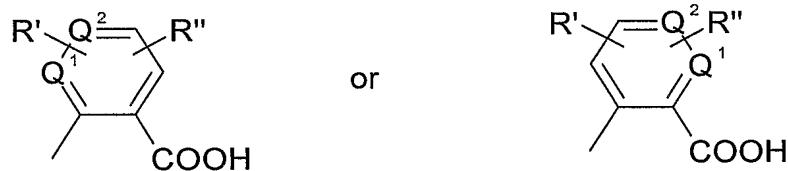
A is C₁₋₆-alkylene, phenylene, or naphthylene wherein the C₁₋₆-alkylene, phenylene, or naphthylene groups may optionally be substituted one or more times with C₁₋₆-alkyl;

5 to form a mixture of the compound of formula (IV) and an ester having the formula



wherein R, Z and Hal is as defined above and V is -CHR'-X-CR''-COOH,

10 -X-CHR''-CO-NH-A-COOH, -CHR''-X-CO-NH-A-COOH,



wherein R', R'', X and A are as defined above;

b) separating the compound of formula (IV) from the ester of formula (V) by a

15 method selected from the group consisting of:

iv) allowing the acid of formula (V) or a salt thereof to precipitate from the reaction mixture, and separating the precipitate of the compound of formula (V) or a salt thereof from the reaction mixture, optionally followed by isolation of the compound of formula (IV) or a salt thereof from the reaction mixture;

v) partitioning between an organic solvent and an aqueous solvent whereby the compound of formula (IV) will be dissolved in the organic phase whereas the compound of formula (V) will be dissolved in the aqueous phase, separating the phases, and optionally isolating the compound of formula (IV)

5 or a salt thereof and/or isolating the compound of formula (V) or a salt thereof; and

vi) adsorbing the compound of formula (V) on a basic resin, separating the solvent containing the compound of formula (IV) from the resin, desorbing the compound of formula (V) from the basic resin, and optionally isolating the compound of formula (IV) or a salt thereof and/or isolating the compound of formula (V) or a salt thereof.

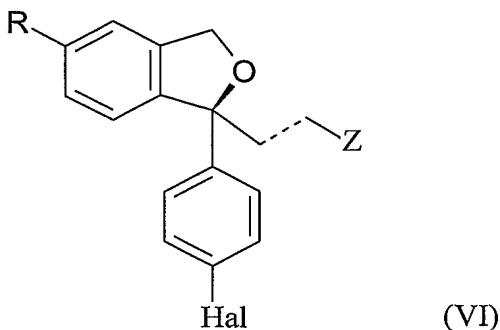
10 2. The method according to claim 1 wherein the separation of the compound of formula (IV) from the ester of formula (V) is performed by allowing the acid of formula (V) to precipitate from the reaction mixture, and separating the precipitate of the compound of formula (V) from the reaction mixture, optionally followed by isolation of the compound of formula (IV) or a salt thereof from the reaction mixture.

15 3. The method according to any of claims 1 or 2 wherein R', R'' and R''' are independently selected from hydrogen and C₁₋₆-alkyl, and Q¹ and Q² are both carbon.

20 4. The method according to any of claims 1-3 wherein the S-enantiomer of the compound of formula (V) or a mixture of enantiomers of the compound of formula (V) comprising more than 50% of the S-enantiomer of the compound of formula (V) is separated from the R-enantiomer of the acyl derivative of formula (IV) or from a mixture of enantiomers of the acyl derivative of formula (IV) comprising more than 50% of the R-enantiomer of the acyl derivative of formula (IV).

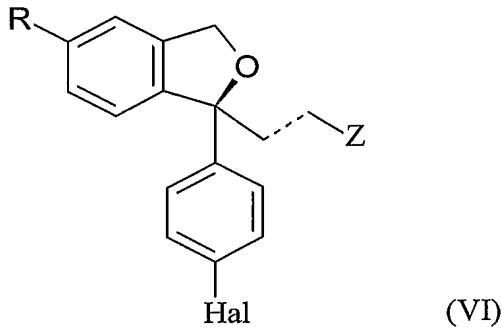
25 5. The method according to claim 4 wherein the S-enantiomer of the compound of formula (V) is separated from the R-enantiomer of the acyl derivative of formula (IV) or from a mixture of enantiomers of the acyl derivative of formula (IV) comprising more than 50% of the R-enantiomer of the acyl derivative of formula (IV).

6. The method according to claim 5 wherein the S-enantiomer of the compound of formula (V) is separated from the R-enantiomer of the acyl derivative of formula (IV).
- 5 7. The method according to any of claims 1-3 wherein the S-enantiomer of the acyl derivative of formula (IV) or a mixture of enantiomers of the acyl derivative of formula (IV) comprising more than 50% of the S-enantiomer of the acyl derivative of formula (IV) is separated from the R-enantiomer of the compound of formula (V) or from a mixture of enantiomers of the compound of formula (V) comprising more than
10 50% of the R-enantiomer of the compound of formula (V).
8. The method according to claim 7 wherein the S-enantiomer of the acyl derivative of formula (IV) is separated from the R-enantiomer of the compound of formula (V) or from a mixture of enantiomers of the compound of formula (V) comprising more
15 than 50% of the R-enantiomer of the compound of formula (V).
9. The method according to claim 8 wherein the S-enantiomer of the acyl derivative of formula (IV) is separated from the R-enantiomer of the compound of formula (V).
- 20 10. The method according to any of claims 4-6 wherein the R group in the compound of formula (V) is obtained in the form of the S-enantiomer is optionally converted to cyano, the Z group in the compound of formula V obtained is optionally converted to a dimethylaminomethyl group, Hal is optionally converted to fluoro, and/or a dotted line representing a double bond is optionally converted to a single bond, in either
25 order, followed by conversion of the compound of formula (V) to escitalopram or a derivative thereof having the formula



wherein R, Z and Hal is as defined above by treatment with a base, optionally followed by, in either order, conversion of the group R to a cyano group, conversion of the group Z to a dimethylaminomethyl group, conversion of Hal to fluoro, and
5 conversion of a dotted line representing a double bond to a single bond; optionally followed by conversion of escitalopram or a derivative of formula (VI) to a salt thereof.

11. The method according to any of claims 7-9 wherein the R group in the compound
10 of formula (IV) the obtained in the form of the S-enantiomer is optionally converted to cyano, the Z group in the compound of formula IV obtained is optionally converted to a dimethylaminomethyl group, Hal is optionally converted to fluoro and/or a dotted line representing a double bond is optionally converted to a single bond, in either order, followed by conversion of the compound of formula (IV) to escitalopram or a
15 derivative thereof



wherein R, Z and Hal is as defined above by treatment with a base, optionally followed by, in either order, conversion of the group R to a cyano group, conversion of the group Z to a dimethylaminomethyl group, conversion of Hal to fluoro, and
20 conversion of a dotted line representing a double bond to a single bond; optionally

followed by conversion of escitalopram or a derivative of formula (VI) to a salt thereof.

12. The method according to any of claims 10 or 11 wherein the basic ring closure is
5 carried out by treatment with a base such as KOC(CH₃)₃ or other alkoxides, NaH or other hydrides, or amines such as triethylamine, ethyldiisopropylamine or pyridine.

13. The method according to any of claims 1-12 wherein Hal is fluoro and R is halogen or cyano, preferred R is cyano.

10

14. The method according to any of claims 1-13 wherein the dotted line represents a single bond.

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15. The method according to any of claims 1-14 wherein and Z is dimethylaminomethyl or a group that may be converted to a dimethylaminomethyl group, preferably Z is a dimethylaminomethyl group.

16. The method according to claims 1-15 wherein the anhydride is a compound of formula (Ia).

20

17. The method according to claim 16 wherein the anhydride is succinic anhydride or glutaric anhydride.

25

18. The method according to claims 1-17 wherein the anhydride is a compound of formula (Ib).

19. The method according to claim 18 wherein the anhydride is phthalic acid anhydride.

30

20. The method according to claims 1-15 wherein the reagent is an imide of Formula (Ic).

21. The method according to claim 20 wherein the imide is N-phenyl-succinimide substituted in the phenyl ring with a carboxy group.
22. The method according to any of claims 1-21 wherein Y in the compound of formula (IV) is a bond.
5
23. The method according to any of claims 1-21 wherein Y in the compound of formula (IV) is O or S.
- 10 24. The method according to claim 23 wherein Y in the compound of formula (IV) is O.
25. The method according to any of claims 1-21 wherein Y in the compound of formula (IV) is NH.
- 15 26. The method according to any of claims 22-25 wherein R¹ is selected from C₁₋₄-alkyl, C₂₋₄-alkenyl and C₂₋₄-alkynyl all of which may optionally be substituted one or more times with substituents selected from C₁₋₄-alkoxy, C₁₋₄-alkylthio, hydroxy, halogen, amino, nitro, cyano, C₁₋₄-alkylamino and di-(C₁₋₄-alkyl)amino.
- 20 27. The method according to claim 26 wherein R¹ is selected from C₁₋₃-alkyl, C₂₋₃-alkenyl and C₂₋₃-alkynyl all of which may optionally be substituted one or more times with substituents selected from C₁₋₃-alkoxy, C₁₋₃-alkylthio, hydroxy, halogen, amino, nitro, cyano, C₁₋₃-alkylamino and di-(C₁₋₃-alkyl)amino.
- 25 28. The method according to claim 26 wherein R¹ is C₁₋₄-alkyl.
29. The method according to claim 27 wherein R¹ is C₁₋₃-alkyl.
- 30 30. The method of claim 29 wherein R¹ is methyl, ethyl or propyl, preferably propyl.

31. The method according to any of claims 1-30 wherein the mixture of a compound of formula (II) and (IV) is prepared by selective enzymatic acylation or selective enzymatic deacylation.

5 32. A method for the manufacture of escitalopram comprising the method of any of claims 1-31.